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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte CHIH-MING CHEN,
JOSEPH CHOU,
and
DAVID WONG,
Appellants

Appeal 2008-5414
Application 09/435,576[1]
Technology Center 1600

Decided: January 26, 2009

Before CAROL A. SPIEGEL, DONALD E. ADAMS, and ERIC GRIMES, *Administrative Patent Judges*.

SPIEGEL, *Administrative Patent Judge.*

DECISION ON APPEAL

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[1] Application 09/435,576 ("the 576 application," the disclosure of which is cited as "Spec."), *HMG-CoA Reductase Inhibitor Extended Release Formulation*, filed 8 November 1999, is a continuation-in-part of application 09/339,494, filed 24 June 1999, now abandoned, which is a continuation of application 08/989,253, filed 12 December 1997, now U.S. Patent 5,916,595. The real parties in interest are said to be ANDRX LABS, LLC and SCIELE PHARMA, INC. (Appellants' Amended Brief on Appeal under 37 C.F.R. § 1.192, filed 27 July 2007 ("App. Br."), 4).

I. Statement of the Case

This is an appeal under 35 U.S.C. § 134 from an Examiner's rejection of all the pending claims, claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71, and 76-81. We have jurisdiction under 35 U.S.C. § 6(b). We AFFIRM.

The subject matter on appeal is directed to a once daily oral cholesterol-lowering drug formulation comprising an alkyl ester of a hydroxy substituted naphthalene derivative, e.g., a statin such as lovastatin, and a controlled release carrier, as well as to its use to lower cholesterol levels in humans. The formulation provides a mean time to peak plasma concentration of the drug of about 10 to about 32 hours after administration. Claims 1 and 70 are illustrative and read (App. Br. 34 and 46, Claims App.):

> 1. A controlled release oral solid dosage form for the reduction of serum cholesterol levels in humans comprising a drug comprising an alkyl ester of hydroxy substituted naphthalenes and a controlled release carrier in an amount effective to provide a controlled release of the drug, the dosage form providing a mean time to maximum plasma concentration (T_{max}) of the drug which occurs at 10 to about 32 hours after oral administration to human patients, the dosage form providing a reduction in serum cholesterol levels when administered to human patients on a once-a-day basis.
>
> 70. A method for improving the dose-response relationship achieved via the administration of a statin drug orally administered in immediate release form, comprising orally administering the statin in a controlled release dosage form which provides a mean time to maximum plasma concentration (T_{max}) of the statin drug which

> occurs at 10 to about 32 hours after oral administration to human patients.

The various independent claims recite a T_{max} after oral administration from (a) 10 to about 32 hours (claims 1, 48, 70, 71), (b) about 11 to about 32 hours (claim 51), (c) 10.4 to about 20.6 hours (claim 58), (d) 10 to about 23.2 hours (claim 62), (e) 9.8 to about 18.8 (14.3 ± 4.5) hours (claims 76, 78), (f) 10.6 to about 23.2 (16.9 ± 6.3) hours (claims 77, 79), and (g) 10.4 to about 20.6 (15.5 ± 5.1) hours (claims 80, 81).

The Examiner has rejected all the pending claims as unpatentable (i) under 35 U.S.C. § 102(b) over Alberts[2] (Ans.[3] 3-4), (ii) under 35 U.S.C. § 103(a) over Chen I[4] alone or in combination with Cheng[5] (Ans. 5-7), and (iii) under obviousness-type double patenting over claims 1-18 of Chen II[6] in combination with Remington[7] (Ans. 7-8).

Appellants rely on Cheng, McClelland[8] and the PDR[9] in support of their arguments.

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[2] U.S. Patent 5,376,383, *Method for Enhancing the Lowering of Plasma-Cholesterol Levels*, issued 27 December 1994, to Alberts et al. ("Alberts").
[3] Examiner's Answer mailed 29 October 2007 ("Ans.").
[4] U.S. Patent 5,837,379, *Once Daily Pharmaceutical Tablet Having a Unitary Core*, issued 17 November 1998, to Chen et al. ("Chen I").
[5] Cheng et al., "Evaluation of Sustained/Controlled-Release Dosage Forms of 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors in Dogs and Humans," *Pharmaceutical Research*, 10 (11): 1683-1687 (1993) ("Cheng").
[6] U.S. Patent 6,485,748 B1, *Once Daily Pharmaceutical Tablet Having a Unitary Core*, issued 26 November 2002, to Chen et al. ("Chen II").
[7] REMINGTON'S PHARMACEUTICAL SCIENCES, Eighteenth Edition, 1990, "Lovastatin," 857-858 ("Remington").
[8] McClelland et al., “Enhancement of 3-Hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitor Efficacy Through

The main issue is whether Appellants have shown the Examiner erred in finding that the applied prior art teaches or suggests a controlled-release drug formulation having the claimed T_{max}.

II. Findings of Fact ("FF")

The following findings of fact, and those set forth in the Discussion, are supported by a preponderance of the evidence of record.

A. Appellants' disclosure

[1] According to the 576 specification, use of 3-hydroxy-3-methylglutaryl-coenzyme A ("HMG-CoA") reductase inhibitors, including alkyl esters of hydroxy substituted naphthalenes such as lovastatin and simvastatin, to reduce serum cholesterol levels is well known (Spec. 1:12-29).

[2] Controlled-release drug formulations, such as osmotic core tablets, are also known (Spec. 2:15-23).

[3] In one embodiment, the 576 specification describes a

> controlled release dosage form . . . preferably prepared by combining . . . simvastatin or lovastatin with a . . . water-swellable polymer and an osmotic agent into a compressed tablet core having an optional first coating for sealing and protection and a second coating comprising a pH sensitive agent water insoluble polymer (Spec. 14:11-15).

[4] Preferred tablet core formulations generally comprise (a) 3-20 wt.% alkyl ester of a substituted naphthalene (HMG-CoA reductase

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Administration of a Controlled-Porosity Osmotic Pump Dosage Form," *Pharmaceutical Research*, 8(7):873-876 (1991) ("McClelland").

[9] THE PHYSICIANS' DESK REFERENCE, 60th edition, Thomson publishers, Montvale, NJ (2006), 2730-2735 ("the PDR").

inhibitor), (b) 10-40 wt.% water swellable polymer, (c) 0.0001 to 0.01 wt.% antioxidant, (d) 20-80 wt.% osmotic agent, (e) 0-5 wt.% surfactant, and (f) 0-5 wt.% lubricant (Spec. 19:5-13).

[5] The water swellable polymer swells and expands in the presence of water to slowly release the HMG-CoA reductase inhibitor (Spec. 15:4-6).

[6] Suitable water swellable polymers include polyethylene oxide, methylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose (Spec. 15:6-13).

[7] The osmotic agent dissolves in water and increases the osmotic pressure inside the core of the tablet (Spec. 14:22-24).

[8] Preferably, the osmotic agent is a simple sugar such as anhydrous lactose (Spec. 14:28-15:2).

[9] Other controlled-release technologies can also be used (Spec. 19:38-20:1), for example the technology described by Chen I (*Id.* at 24:11-12).

B. Alberts

[10] Alberts discloses a controlled-release cholesterol lowering drug formulation comprising an HMG-CoA reductase inhibitor and a carrier which releases the inhibitor over a period of 6 to 24 hours (Alberts 2:54-66).

[11] According to Alberts, a variety of known controlled-release formulations may be used, including diffusion controlled systems, osmotic devices, dissolution controlled matrices and erodible/degradable matrices (Alberts 2:66-3:5).

[12] One embodiment of a controlled-release formulation comprises a core composition containing a diffusible water soluble HMG-CoA reductase inhibitor and an osmotically effective agent surrounded by a water insoluble wall prepared from a polymer material that is permeable to water but substantially impermeable to solute (i.e., water swellable) (Alberts 3:6-16).

[13] Example 10 describes a formulation having a core composition comprising about 15 wt.% lovastatin, about 28.6 wt. % lactose (osmotic agent), about 32 wt.% Klucel LF + Methocell K15M (water swellable polymers), about 0.015 wt.% butylated hydroxyanisol (antioxidant), about 0.9 wt.% magnesium stearate (lubricant), and about 23.5 wt.% SD3A (alcohol solvent) (Alberts 10:1-11).

[14] Eighty-five % of the lovastatin in Example 10 was released over 18 hours (Alberts 10:13-15).

[15] Alberts is silent regarding the T_{max} of its formulations.

C. Chen I

[16] Chen I discloses a controlled-release tablet having a core composition comprising a medicament, one or more osmotic polymers, and a water soluble osmotic agent, wherein the core is subsequently coated with a modified polymeric membrane to provide therapeutic blood levels of the medicament with once a day administration (Chen I 1:66-2:15; 3:28-43).

[17] If two osmotic polymers are used in the core composition, the first osmotic polymer may be a water soluble polymer, e.g., polyvinyl pyrrolidine having a weight average molecular weight of 25,000 to 200,000, while the second osmotic polymer may be a water swellable

polymer, e.g., polyethylene oxide having a weight average molecular weight of 100,000 to 6,000,000, hydroxypropyl methylcellulose, and the like (Chen I 4:24-30 and 37-64).

[18] The first water soluble polymer will generally be from about 15 to about 40% based on the weight of the compressed core, while the second water swellable polymer will generally be from about 5 to about 15% based on the weight of the compressed core (Chen I 4:31-36 and 4:64-5:2).

[19] Exemplary medicaments include HMG CoA reductase inhibitors, i.e., lovastatin, fluvastatin, simvastatin, and pravastatin (Chen I 2:51-65)

[20] Preferred osmotic agents include sucrose, lactose, dextrose, sodium chloride and potassium chloride (Chen I 4:16-19).

[21] Exemplary osmotic polymers include water soluble polyvinyl pyrrolidone (e.g., povidone), hydroxypropyl cellulose, polyethylene oxide, and hydroxypropyl methylcellulose (Chen I 4:24-61).

[22] The core composition of Example 2 of Chen I comprises 10.5 wt.% nifedipine (medicament), 45.5 wt.% anhydrous lactose (osmotic agent), 1.9 wt.% sodium lauryl sulfate (surfactant), 10.5 wt.% poly(ethyleneoxide) having an approximate molecular weight of 5,000,000 (water swellable polymer) and 31.6 wt.% povidone having a weight average molecular weight of about 50,000 (water soluble polymer) (Chen I 7:31-44).

[23] Chen I is silent regarding the T_{max} of the formulation of Example 2.

D. Cheng

[24] Cheng discloses seven sustained-release (SR) or controlled-release (CRS) formulations for oral delivery of lovastatin or simvastatin (Cheng abstract).

[25] Cheng discloses an embodiment comprising a controlled-release coated tablet containing 40 mg of lovastatin from which approximately 80% of the drug is released from the tablet in about 14 hours (CRS14) (Cheng 1683, ¶ 2; 1684, ¶ 1; 1685, ¶ 3). The release of the drug is controlled by the coat (Cheng 1683, ¶ 2).

[26] Dogs receiving a single 80 mg dose of lovastatin, i.e., 2 tablets, in the CRS14 formulation showed a T_{max} of 7.5 ± 1.2 hours (Cheng 1685, Table II).

[27] According to Cheng, CRS formulations provided *in vivo* plasma profiles consistent with *in vitro* data and were as effective as conventional tablet formulations in lowering the dogs' cholesterol levels (Cheng 1686, ¶ 5 and Table IV).

[28] Cheng discloses another embodiment comprising a 14 hour sustained release matrix tablet formulation, SRT14, containing 40 mg of lovastatin, which released approximately 90% of the drug over a 14 hour period (Cheng 1683, ¶ 2; 1684, ¶ 1; 1685, ¶ 3). The release of the drug was controlled by the matrix (Cheng 1683, ¶ 2).

[29] Dogs receiving a single 80 mg dose of lovastatin, i.e., 2 tablets, in the SRT14 formulation showed a T_{max} of 2.3 ± 0.8 hours (Cheng 1685, Table II).

E. Chen II

[30] Claim 1 of Chen II (Chen II 8:61-9:8) reads:

> A controlled release tablet which comprises:
>
> (a) a homogeneous compressed core which comprises:
> (i) a medicament which is very slightly soluble to practically insoluble in water at 25° C.;
> (ii) a water soluble osmotic compound[;],
> (iii) one or more osmotic polymers which comprise poly(ethylene oxide); and
>
> (b) a membrane coating which completely covers said core tablet which comprises a mixture of a:
> (i) a water insoluble pharmaceutically acceptable polymer; and
> (ii) a pH dependent polymer such as an enteric coating polymer, the weight ratio of the pH dependent polymer to the water insoluble pharmaceutically acceptable polymer being 0.1:1 to 0.75:1.

F. Remington

[31] According to Remington, lovastatin is insoluble in water and sparingly soluble in alcohol (Remington 857-858).

G. McClelland

[32] McClelland discloses a controlled-release formulation containing simvastatin and a tromethammonium osmotic pump, and has a T_{max} of less than 5 hours (McClelland abstract; 875, Fig. 2).

H. PDR

[33] The PDR describes an extended-release formulation (Lescol® XL) comprising fluvastatin, microcrystalline cellulose, hydroxypropyl

cellulose, hydroxypropyl methyl cellulose, potassium bicarbonate, povidone (PVP), and magnesium stearate (PDR 2730, last ¶).

[34] According to the PDR, Lescol® XL has an average T_{max} between about 2.5 to 3 hours (PDR 2731, Table 1).

III. Discussion

A. Rejection of claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71, and 76-81 under § 102(b) over Alberts

1. The Examiner's findings

The Examiner found the formulation of Example 10 of Alberts is not only substantially similar to the preferred composition disclosed in Table 1 of the 576 specification, but also has the same intended purpose of releasing an effective amount of HMG-CoA reductase inhibitor into the blood in a controlled manner (Ans. 3-4 and 10-11). The Examiner found that Alberts disclosed Example 10 as having a controlled drug release over an 18 hour period, but did not disclose its T_{max} (Ans. 4). However, according to the Examiner, the claimed T_{max} is inherent in Example 10 because its formulation is substantially similar to the preferred composition disclosed in Table 1 of the 576 specification (Ans. 4).

2. Appellants' position

Appellants argue that the claimed T_{max} limitations are not inherent in Alberts' formulations (App. Br. 18-19). Appellants contend that Alberts' Example 3 has a formulation that is virtually identical to the formulation disclosed by McClelland which is said to have a T_{max} of less than 5 hours (App. Br. 19). Appellants also contend the PDR discloses a once daily controlled-release statin formulation, Lescol® XL, which is said to have a

T_{max} of 2.5 to 3 hours (App. Br. 21). Therefore, Appellants contend Alberts does not necessarily disclose the claimed T_{max} limitations (App. Br. 19-21).

Appellants further argue that percentage drug release over time does not necessarily correlate to T_{max} (App. Br. 20; Reply Br.[10] 5-6). According to Appellants, SRT14 of Cheng and Example 10 of Alberts are similar swellable matrix formulations of lovastatin which release 90% and 85% of the statin, respectively, over a 14 hour and an 18 hour time period, respectively (Reply Br. 5). However, Table II of Cheng indicates that SRT14 has a T_{max} of 2.3 hours (Reply Br. 5).

Appellants still further argue "that the claims are not meant to encompass any formulation that may fall within the general ranges of Table I of the present application. . . . The exemplified formulations which exhibit the pharmacokinetic data of the instant claims contain a core, a seal coat, an inner coating containing an enteric polymer, an outer coating containing an enteric polymer and a water insoluble polymer, and an optional overcoat. . . ." (App. Br. 22). "In contrast, Alberts describes tablets with cores that **do not** contain water swellable polymers (examples 3-7) and tablets that contain drug mixed with a water swellable polymer, but **do not** have an outer coating containing an enteric polymer and a water-insoluble polymer (examples 8-16)" (App. Br. 22, original emphasis).

Finally, Appellants contend Alberts does not teach or suggest that use of the claimed controlled-release formulation provides an improved dose-response relationship or improved bioavailability vis-à-vis use of an immediate release formulation as recited in claims 70 and 71; or, the dissolution parameters recited in claim 71 (App. Br. 22).

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[10] Reply to Examiner's Answer filed 29 November 2007 ("Reply Br.").

3. Legal principles

A prior art reference must disclose every limitation of the claimed invention, either expressly or inherently, to anticipate. *In re Schrieber*, 128 F.3d 1473, 1477 (Fed. Cir. 1997). Where the claimed and prior art products and processes are identical or substantially identical, the burden is on Appellants to prove otherwise. *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977); *In re Spada*, 911 F.2d 705, 709 (Fed. Cir. 1990); *In re Fitzgerald*, 619 F.2d 67, 70 (CCPA 1980). Furthermore, '"particular limitations or embodiments appearing in the specification [generally] will not be read into the claims.'" *Eneron GmbH v. ITC*, 151 F.3d 1376, 1384 (Fed. Cir. 1998) (quoting *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 867 (Fed. Cir. 1985)).

4. Analysis

Here, the controlled-release formulation of Example 10 of Alberts appears identical or substantially identical to preferred controlled-release formulations described in the 576 specification (FF 3, 4, and 13) and is useful for the same purpose of lowering a patient's blood cholesterol level by supplying a therapeutic level of statin over time (FF 1 and 10). Thus, it is appropriate to shift the burden to Appellants to show otherwise. Appellants have failed to meet their burden.

The Examiner's *prima facie* case of anticipation is based specifically on Example 10 of Alberts. The argument that Example 3 of Alberts does not have a T_{max} in the claimed range as allegedly shown by McClelland is not directed to the anticipatory prior art formulation and, therefore, is not persuasive. Similarly, arguments based on PDR's Lescol® XL and Cheng's SRT14 formulations are not persuasive because Appellants have failed to

establish that either of these formulations are the same as Example 10 of Alberts. For example, Appellants have not shown that the Lescol® XL formulation contains an osmotic agent as is contained in Example 10 (FF 13 and 33). Similarly, Appellants have not described the components of Cheng's SRT14 formulation and their concentrations. Furthermore, Appellants have failed to identify any claim on appeal requiring a controlled-release formulation having an outer coating containing an enteric polymer and a water-insoluble polymer. It is improper to read selected limitations or embodiments appearing in the supporting specification into a claim without basis. To the contrary, the 576 specification indicates outer coatings are optional (see e.g., FF 3 and 4). Therefore, these arguments are not persuasive.

Finally, as pointed out by the Examiner (Ans. 3-4), an improved dose-response relationship with reduced potential side effects is a major reason for utilizing controlled-release dosage formulations to begin with.

[36] As stated by Alberts,

> [u]tilizing controlled or sustained release technologies, a single administration of the indicated daily dosage amount delivers the drug to the patient over an extended period of time (i.e. 6 to 24 hours) to yield an equivalent or improved therapeutic effect while lowering the peak drug plasma levels (Alberts 1:44-49).

In addition, since lovastatin hydrolyzes to its acid form *in vivo*, one of ordinary skill in the art would have reasonably expected a controlled release of a given amount of lovastatin over time to result in a lower bioavailability of lovastatin acid vis-à-vis a bolus dose of lovastatin (see Ans. 4). As to the dissolution rates recited in claim 71, insofar as the formulation of Example

10 of Alberts appears identical or substantially identical to preferred controlled-release formulations described in the 576 specification, it is appropriate to shift the burden to Appellants to establish that the Example 10 formulation does not possess the claimed dissolution rates. We note that claim 71 recites, in part, a release of not less than about 75% of lovastatin after 16 hours, while 85% of the lovastatin in Example 10 of Alberts was released after 18 hours (FF 14).

In summary, the Examiner has established a factual basis to show Example 10 of Alberts is substantially identical to the claimed controlled-release product in both formulation and method of use sufficient to shift the burden to Appellants to prove that Example 10 does not inherently possess the claimed T_{max} and other pharmacokinetic properties. Appellants have failed to rebut the Examiner's *prima facie* finding of anticipation for the reasons given. Therefore, the rejection of claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71, and 76-81 under § 102(b) over Alberts is sustained.

B. Rejection of claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71, and 76-81 under § 103(a) over Chen I alone or in combination with Cheng

1. The Examiner's findings and conclusions

The Examiner found that Example 2 in Chen I exemplifies a controlled-release matrix device that is substantially identical to the preferred controlled-release matrix device described in Table 1 and Example 3 of the 576 specification (Ans. 5). Specifically, the Examiner found (Ans. 16-18):

Instant Invention: Table 1 **General Formula**	**Inventive Example 3** **Specific Formula**	**Prior Art Example 2**
Core:	**Core:**	**Core:**
Alkyl ester of a substituted naphthalene 3-20%	Lovastatin 12.14%	Nifedipine 10.5%
Water swellable polymer 10- 40%	Polyox WSR Coagulant, 4.53% Polyox WSR N 80, 17.76% Polyox (Polyethylene Oxide)	Polyethylene Oxide 10.5%
Antioxidant 0.001-0.01%	BHT 0.03%	-
Osmotic agents 20-80%	Lactose 51.30%	Lactose (75.2g) 45.5%
Surfactant 0-5%	Sodium Lauryl Sulfate 3.04%	Sodium Lauryl Sulfate 1.9%
Lubricant 0-5%	Silicone dioxide 0.46% Glyceryl Monostearate 1.82%	-

Seal Coating 0-10	**Seal Coating** Opadry Clear	**Color Coating** 4% See column 8, line 16. Opadry Yellow
Osmotic Agent 0-10	Sodium Chloride	Sodium Chloride
Inner Coating	**Inner Coating**	**Inner Coating**
Enteric Polymer 0-30%	-	-
Anti-Sticking Agent 0-6%	-	-
Plasticizers 0-6%	-	-
Channeling Agent 0-6%	-	-
Outer Coating:	**Outer Coating:**	**Sustained Release Coating (only 2% applied, which reduces the weight % in composition to be similar to instant weight %)**
Blend of Enteric Polymer and Water-insoluble Polymer 0.5-5%	Cellulose Acetate 1.43% Eudragit S 100 0.49%	Cellulose Acetate 60% Eudragit S 100 20%
Plasticizers 0-1%	Triacetin 0.11% PEG 400 0.11%	Triacetin 5% PEG 400 5%
Channeling Agent 0.2-5%	Sugar 0.72%	Sucrose 10%
Overcoat	**Overcoat**	**Enteric Coating (2-5%**

		applied, which reduces the weight % in composition to be similar to instant weight %)
Enteric Polymer 0-30%	HPMC 0.77%	HPMCP 70%
Anti-Sticking Agent 0-6%	Talc 0.30%	Talc 23%
Plasticizers 0-6%	Triacetin 0.12%	Acetyltributyl Citrate 7%
Channeling Agent 0-6%	Sugar 0.30%	Pore Forming Agent 5-25% or 0-30%

The Examiner acknowledged that the formulation of Example 2 in Chen I differs in containing a nifedipine medicament instead of an alkyl ester of a substituted naphthalene, e.g., lovastatin, as described in Table 1 and Example 3 of the 576 specification (Ans. 5 and 18). The Examiner found Chen I did not disclose the pharmacokinetic parameters of Example 2, e.g., its T_{max} (Ans. 5). However, since Chen I disclosed lovastatin as a suitable medicament for use with its controlled-release matrix, the Examiner concluded it would have been obvious to formulate lovastatin in the controlled-release matrix of Chen I to obtain the benefits of controlled release technology (Ans. 6). According to the Examiner, a controlled-release formulation according to Example 2 of Chen I would have reasonably been expected to exhibit the claimed pharmacokinetic parameters since its controlled-release matrix is substantially similar to the controlled-release matrix described in Table 1 and Example 3 of the 576 specification, regardless of the medicament used in the formulation (Ans. 6-7 and 26).

Alternatively, the Examiner found Cheng teaches controlled- and sustained-release formulations containing lovastatin for the treatment of hypercholesterolemia (Ans. 6). The Examiner concluded it would have been obvious to use lovastatin as the medicament in the controlled release formulation of Chen I because Cheng teaches the use and benefits of lovastatin in a modified release formulation for reducing cholesterol levels in humans (Ans. 7). In addition, the Examiner found Cheng discloses pharmacokinetic data obtained from dogs receiving 80 mg of lovastatin in various modified release formulations (Ans. 6), including a T_{max} of 8.7 hours with the CRS14 formulation (*id.* at 24). According to the Examiner, "it is conventional in the pharmaceutical research to draw conclusions from animal models and apply them to humans" (Ans. 7).

2. Appellants' position

Appellants reiterate several of the arguments raised against Alberts. In particular, Appellants repeat the arguments based on the PDR (Lescol® XL), on the improved dose-response relationship or improved bioavailability recited in claims 70 and 71, and on the dissolution parameters recited in claim 71 (App. Br. 25-26 and 30). In addition, Appellants argue it is improper to base an obviousness rejection on an alleged inherent property of the prior art (App. Br. 25-27; Reply Br. 6). Appellants further argue that Chen I does not provide any reason to select lovastatin from its sizable lists of suitable medicaments and that the lack of structural similarity between lovastatin and nifedipine makes prediction of pharmacokinetic data from one drug formulation to the other drug formulation unpredictable (App. Br. 28-30).

3. Legal principles

A claimed invention is not patentable if its subject matter would have been obvious to a person of ordinary skill in the art. 35 U.S.C. § 103(a); *KSR Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007); *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). Facts relevant to a determination of obviousness include (1) the scope and content of the prior art, (2) any differences between the claimed invention and the prior art, (3) the level of ordinary skill in the prior art, and (4) relevant objective evidence of obviousness or non-obviousness. *KSR*, 127 S.Ct. at 1734; *Graham*, 383 U.S. at 17-18. Further, a person of ordinary skill in the art uses known elements and process steps for their intended purpose. *Anderson's-Black Rock, Inc. v. Pavement Salvage Co.*, 396 U.S. 57, 90 S.Ct. 305 (1969); *Sakraida v. AG Pro, Inc.*, 425 U.S. 273, 282, 96 S.Ct. 1532 (1976); *Dunbar v. Myers*, 4 Otto (94 U.S.) 187, 195 (1876). The question to be asked is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR,* 127 S. Ct. at 1740. The Supreme Court also noted in *KSR* that an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 127 S. Ct. at 1741.

4. Analysis

Here, the Examiner's conclusion of obviousness is based on using a known controlled-release matrix for its intended purpose of providing a controlled release of a water insoluble medicament at therapeutic dose levels. The core composition of Example 2 contains two osmotic polymers, including 10.5 wt.% polyethylene oxide, a water swellable polymer (FF 16-

18). Appellants have not challenged the Examiner's finding that polyethylene oxide is a water swellable polymer as that term is used in the 576 specification. Table 1 of the 576 specification illustrates preferred core compositions of the claimed invention containing 10-40 wt.% water swellable polymer (FF 4). According to Appellants, the claims are meant to encompass not only any formulation falling within the general ranges of Table 1 of the 576 specification, but also those formulations which exhibit the claimed T_{max} parameters (App. Br. 22).

As pointed out by the Examiner (Ans. 21), the 576 specification expressly identifies Chen I (i.e., U.S. Patent No. 5,837,379) as a "specific controlled release technolog[y] which may be used in conjunction with the present invention" (Spec. 24:11-12). In addition, the Examiner has provided a detailed comparison of Example 2 of Chen I and inventive examples of the '576 specification indicating their respective controlled release devices are substantially similar (Ans. 16-18). Therefore, the Examiner has provided a reasonable basis for concluding the controlled release technology of Chen I would provide formulations having substantially similar pharmacokinetics, including a T_{max} within the claimed ranges.

Appellants' arguments based on different controlled release formulations, e.g., the controlled release formulation found in Lescol® XL, which does not appear to contain an osmotic agent as found in Chen I are not persuasive. Furthermore as stated above, since lovastatin hydrolyzes to its acid form *in vivo*, controlled release of a given dose of lovastatin over time would be expected to result in a lower bioavailability of lovastatin vis-à-vis a bolus dose of lovastatin (see Ans. 4). Similarly, Chen I suggests a controlled release formulation having pharmacokinetics which may

optimized to obtain a desired therapeutic drug level over a desired time period.,

Arguments based on a lack of motivation to select lovastatin as the medicament incorporated into Chen I's controlled release formulation are also unpersuasive. Chen I explicitly suggests statins, e.g., lovastatin, as suitable drugs for formulation using its controlled release (FF 17). While the exemplified nifedipine and the suggested statin are different drugs with different structures, Chen I teaches that its controlled release formulation is generically applicable to "medicaments which are water soluble to practically insoluble in water" (Chen I 2:44-45). Notably, while Appellants have argued that the differences in structure, pharmacological properties, and characteristics of the medicament used would be considered by one of ordinary skill in the art in preparing a controlled release formulation (App. Br. 30), Appellants have not argued that it was beyond ordinary skill in the art to prepare a formulation for a particular drug. Thus, the situation here is more properly characterized as one of optimizing result-effective variables "to maintain therapeutic serum levels . . . and to minimize the effects of missed doses . . . caused by a lack of patient compliance" (Chen I 1:8-11) in view of those differences in structure and pharmacological properties and characteristics of the drug, e.g., sensitivity to pH, metabolites produced *in vivo*, etc.

In short, the Examiner has provided a sufficient factual basis to support a *prima facie* conclusion of obviousness which the Appellants have failed to rebut with persuasive arguments or secondary evidence. Therefore, we sustain the rejection of claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71

and 76-81 under § 103(a) over Chen I. Hence, it is unnecessary for us to consider the combined teachings of Chen I and Cheng.

C. Rejection of claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 under obviousness-type double patenting over claims 1-18 of Chen II in combination with Remington

1. The Examiner's findings and conclusion

According to the Examiner, Chen II claims "a controlled release oral solid dosage form containing a compressed core with a slightly soluble to practically insoluble in water medicament and a membrane coating" (Ans. 8). The Examiner found that Remington teaches lovastatin is insoluble in water (Ans. 8). More specifically, the Examiner determined the difference between the claims is that the claims on appeal recite a functionally defined controlled release formulation containing a specific species of practically water insoluble medicament, whereas the patented claims of Chen II structurally recite the same controlled release formulation containing a generic practically water insoluble medicament (Ans. 28). Therefore, the Examiner concluded the claims on appeal are obvious over claims 1-18 of Chen II (Ans. 8).

2. Appellants' position

Appellants argue the claims of Chen II fail to teach, suggest, or hint at the T_{max} ranges, alkyl esters of hydroxyl substituted naphthalenes, or lovastatin recited in the appealed claims (App. Br. 31-32). Appellants further argue that the Chen II claims do not teach or suggest that sustained release statin formulations having a T_{max} of 10 to about 32 hours unexpectedly yield increased total statin blood concentrations and lower peak levels of the statin's acid metabolite (Reply Br. 9).

3. Legal principles

"Obviousness-type double-patenting is a judge-made doctrine that prevents an extension of the patent right beyond the statutory time limit. It requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent." *In re Berg*, 140 F.3d 1428, 1431 (Fed. Cir. 1998).

4. Analysis

Here, we agree with the Examiner that the difference between the claims is that the claims on appeal recite a functionally defined controlled release formulation containing a specific species of a practically water insoluble medicament, whereas the patented claims of Chen II structurally define the same controlled release formulation containing a generic practically water insoluble medicament. Remington discloses that lovastatin is a water insoluble medicament (FF 31). Therefore, the claims on appeal are *prima facie* an obvious species of the invention claimed in Chen II.

Allegations that the claims on appeal provide results which are unexpected from the claims of Chen II lack a factual basis. To wit, a controlled release formulation by definition releases smaller amounts of its dosed drug over a sustained time period than an immediate release formulation which provides its dosed drug as essentially a single bolus at once. Thus, one of ordinary skill in the art would have reasonably expected a controlled release formulation to have more drug available, as time passed, for treatment. Similarly, since more of a drug is released from an immediate release formulation than from a controlled release formulation, the immediate release formulation would reasonably be expected to yield a

higher peak metabolite concentration *in vivo* since there is more parent drug available for metabolism.

Therefore, we sustain the rejection of claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 under obviousness-type double patenting over claims 1-2 of Chen II combined with Remington.

IV. Order

Upon consideration of the record, and for the reasons given, it is

ORDERED that the decision of the Examiner rejecting claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 as unpatentable under 35 U.S.C. § 102(b) over Alberts is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner rejecting claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 as unpatentable under 35 U.S.C. § 103(a) over Chen I alone or in view of Cheng is AFFIRMED;

FURTHER ORDERED that the decision of the Examiner rejecting claims 1-13, 18, 19, 21, 22, 25-29, 31-54, 57-71 and 76-81 as unpatentable under obviousness-type double patenting over claims 1-12 of Chen II in combination with Remington is AFFIRMED; and,

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

rvb

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